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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,677	08/01/2001	Brett P. Monia	RTS-0245	7100

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Jane Massey Licata
Licata & Tyrrell, P.C.
66 East Main Street
Marlton, NJ 08053

EXAMINER	
LACOURCIERE, KAREN A	
ART UNIT	**PAPER NUMBER**
1635	5

DATE MAILED: 05/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No.	Applicant(s)	
	09/920,677	MONIA ET AL.	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 5-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2 and 5-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

In response to the restriction requirement set forth in the prior Office action (mailed 03-05-2003) Applicant has canceled claims drawn to multiple, specific SEQ ID NO:'s and has limited the claimed invention to antisense targeted to a nucleic acid of SEQ ID NO:3, which renders the restriction requirement moot. Applicant traverses the restriction requirement and argues that the restriction requirement is improper because the each of the sequences recited in canceled claims 3 and 4 share the ability to modulate a common structure, p70 s6 kinase and therefore the sequences are not distinct and would not pose an undue burden on the office. These arguments are not found to be persuasive because each sequence has a distinct structure, that is to say a unique nucleotide sequence, and the search for each of those sequences would be a separate and distinct search and constitutes an undue burden on the office.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2 and 5-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it recites an antisense compound that "specifically hybridizes with", but does not indicate what the antisense compound hybridizes with. It

is unclear, for example, if the antisense hybridizes with the nucleic acid encoding p70 S6 kinase, the protein product of the nucleic acid encoding p70 S6 kinase or another cellular component, for example, another nucleic acid. Claims 2 and 5-20 are indefinite for the same reasons, due to dependence on claim 1.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-20 are rejected under 35 U.S.C. 112; first paragraph, because the specification, while being enabling for *in vitro* (cell culture) inhibition of p70 s6 kinase (SEQ ID NO:3) expression using antisense, does not reasonably provide enablement for *in vivo* (whole organism) methods of treatment using antisense targeted to p70 s6 kinase (SEQ ID NO:3). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 16-20 are drawn broadly to inhibition of the expression of s p70 s6 kinase (SEQ ID NO:3) in any cell *in vivo* (whole organism) for the treatment of any disease that is associated with p70 s6 kinase. Claims 18-20 are further drawn to treating any hyperproliferative disorder, including any form of cancer, or metabolic disorder associated with p70 s6 kinase using antisense targeted to a nucleic acid encoding p70 s6 kinase (SEQ ID NO:3).

The specification provides examples wherein phosphorothioate and chimeric phosphorothioate antisense targeted to a nucleic acid encoding p70 s6 kinase (SEQ ID NO:3) inhibited the expression p70 s6 kinase *in vitro* (cell culture) in human cell lines. The specification does not demonstrate any correlation with the inhibition of p70 s6 kinase in cell culture and a treatment effect for any disease or condition associated with p70 s6 kinase. The specification does not present any examples wherein antisense targeted to p70 s6 kinase (SEQ ID NO:3) was delivered to cells *in vivo* (whole organism), nor wherein antisense targeted to p70 s6 kinase(SEQ ID NO:3) inhibited the expression of p70 s6 kinase in cells *in vivo* (whole organism). The specification does not provide any examples wherein treatment effects were obtained for any disease or condition, including a hyperproliferative disorder, including cancer, or a metabolic disorder using antisense targeted to p70 s6 kinase (SEQ ID NO:3).

The specification does not present any guidance on what specific diseases or conditions can be treated using antisense targeted to p70 s6 kinase, including specific hyperproliferative disorders or metabolic disorders, and what cells to target for a particular disease or condition.

At the time the instant invention was made, the therapeutic use of antisense oligonucleotides was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of antisense *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, Vol 6, p 72-81, February 2000), Branch (TIBS 23, Feb 1998, p45-50), Green et al. (J. Am Coll. Surg., Vol 191, No. 1, July 2000, p 93-105), Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonantisense effects. Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNs and ribozymes is the problem of delivery....Presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Green et al. state, "It is clear that the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense ODNs can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established....Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo*, with a resultant therapeutic outcome, as claimed. The specification provides examples wherein antisense is delivered to cells *in vitro* and the expression of p70 s6 kinase is inhibited, however, cell culture examples are generally not predictive of *in vivo* inhibition due to differences in metabolites and clearance rates, local concentration of antisense, differences in target site accessibility, cellular uptake differences and the potential for non-antisense side effects. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism) (see for example Jen et al., page 313, second column, second paragraph). For example, Agrawal et al. (see p 79-80, section entitled *Cellular uptake facilitators for in vitro studies*) states "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....In vitro, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

The field of antisense, to date, does not provide guidelines by which antisense can be routinely delivered to generally any cell type *in vivo* (whole organism) at a concentration effective to result in a predictable therapeutic effect. The specification does not provide specific guidance by which one skilled in the art would expect to be

able to deliver antisense targeted to p70 s6 kinase (SEQ ID NO:3) to generally any target cell or tissue *in vivo* (whole organism) at a concentration effective to provide a pharmaceutical effect or to treat the broad range of diseases encompassed by the claims.

In order to practice the invention claimed, over the full scope claimed, one skilled in the art would need to undergo undue trial and error experimentation, beyond the teachings of the instant specification. The quantity of undue experimentation would include the determination of what specific diseases and conditions can be treated by the inhibition of the expression of p70 s6 kinase, what specific cells to target with p70 s6 kinase antisense for the treatment of a particular disease or condition, and how to specifically deliver antisense to a target cell *in vivo* (whole organism) at a concentration effective to result in inhibition of the expression of p70 s6 kinase to a level sufficient to result in a pharmaceutical effect or to treat a disease. Additionally, this undue experimentation would include the determination of such factors as dosage, route of administration, disposition of the antisense molecule in tissues, and the half life and stability of the antisense molecule *in vivo*. Given the art recognized unpredictability of the therapeutic application of antisense *in vivo* (whole organism), this determination would not be routine and would require undue trial and error experimentation.

Therefore, due to the broad scope of the methods of treatment claimed, the state of the art of antisense, the level of unpredictability of *in vivo* (whole organism) methods of treatment using antisense, the lack of specific guidance for the *in vivo* (whole organism) application of antisense methods of treatment and the lack of working

examples or examples which correlate with the claimed methods, one skilled in the art would not be able to practice the methods of claims 16-20 over the full scope claimed without undue trial and error experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 7, 9-13, 15 and 16 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Shimkets et al. (WO 01/47944). Applicant should note, Shimkets has only been provided in part, because the full document exceeds 4000 pages. The relevant portions of the document, applied in the rejection set forth below, have been provided, including the abstract and full description pages. The remainder of the document is the sequence listing. The sequence of the oligonucleotides applied in the rejection has been attached as an alignment with the instantly disclosed SEQ ID NO:3. The complete 4144 pages will be provided only at Applicants request.

Shimkets et al. disclose oligonucleotides 50 nucleobases in length complementary to SEQ ID NO:3 at residues 1610-1659 (SEQ ID NO:2049 of Shimkets

et al.) and residues 1655-1706 (SEQ ID NO:2047 and 2048 of Shimkets et al.). Shimkets et al. disclose these sequences as Single Nucleotide Polymorphisms and disclose antisense targeted to the complement of these sequences (see for example p24-27 of Shimkets et al.). Shimkets et al. disclose this antisense as comprising modifications that enhance the biological stability or physical stability of the oligonucleotides, including a modified sugar (e.g. 2'-o-methylribonucleotide, see page 26) or a modified base, including 5-methylcytosine (see, for example, paragraph bridging p 25-26). Shimkets et al. discloses their antisense as chimeric RNA-DNA antisense (see for example p 27). Shimkets et al. disclose administering antisense to cells and tissues for the inhibition of the expression of a target nucleic acid, which would necessitate that the antisense be in a composition comprising a pharmaceutically acceptable diluent, e.g. water. Shimkets et al. do not explicitly state that their antisense targets and inhibits the expression of p70 s6 kinase, however, the antisense disclosed by Shimkets et al. meets all of the physical limitations of the instantly claimed antisense and, therefore, would be expected to inherently inhibit the expression of p70 s6 kinase. Therefore, Shimkets et al. anticipates claims 1, 2, 7, 9-13, 15 and 16.

Claims 1, 2, 12, 13 and 15 are rejected under 35 U.S.C. 102(e) as being anticipated by Plowman et al. (WO 01/77338).

Plowman et al. disclose a 25-mer oligonucleotide fully complementary to residues 1087-1111 of SEQ ID NO:3 (see for example, page 104, example 2b, SGK351 primer #2). Plowman et al. disclose their oligonucleotide in a composition comprising a

pharmaceutically acceptable diluent, for example, water. Plowman et al. disclose their oligonucleotide as a primer, however, the oligonucleotide meets all of the physical limitations of the instantly claimed oligonucleotide and, therefore, would be expected to hybridize to SEQ ID NO:3 and act as an antisense oligonucleotide to inhibit the expression of p70 s6 kinase. Therefore, Plowman et al. anticipates claims 1, 2, 12, 13 and 15.

Claims 1, 2 and 12-16 are rejected under 35 U.S.C. 102(a) as being anticipated by Yang et al. (Endocrinology 142(8): 3502-3511).

Yang et al. disclose a 21-mer antisense oligonucleotide targeted to a nucleic acid encoding p70 s6 kinase (SEQ ID NO:3) (see for example (p 3503, last paragraph, to p 3505) and further disclose using this antisense in a composition comprising a colloidal dispersion system, lipofectin, to inhibit the expression of p70 s6 kinase in cells in vitro.

Therefore, Yang et al. anticipates claims 1, 2 and 12-16.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2 and 5-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shimkets et al. (WO 01/47944) in view of Baracchini et al. (US Patent No. 5,801,154).

Claims 1, 2 and 5-16 are drawn to an antisense compound 8-50 nucleotides in length targeted to a nucleic acid encoding p70 s6 kinase (SEQ ID NO:3), wherein the antisense comprises modified bases, including 5-methylcytosine modifications, modified sugars, including 2'-O-methoxyethyl modifications, internucleoside linkage modifications, including phosphorothioate, chimeric antisense, and compositions comprising said antisense and a pharmaceutically acceptable carrier, including a colloidal dispersion system. The claims are further drawn to methods to inhibit the expression of p70 s6 kinase in cells *in vitro*.

Shimkets et al. teach oligonucleotides 50 nucleobases in length complementary to SEQ ID NO:3 at residues 1610-1659 (SEQ ID NO:2049 of Shimkets et al.) and residues 1655-1706 (SEQ ID NO:2047 and 2048 of Shimkets et al.). Shimkets et al. teach these sequences as Single Nucleotide Polymorphisms and disclose antisense targeted to the complement of these sequences (see for example p24-27 of Shimkets et

al.) and teach incorporating modifications that enhance the biological stability or physical stability of the oligonucleotides, including a modified sugar (e.g. 2'-o-methylribonucleotide, see page 26) or a modified base, including 5-methylcytosine (see, for example, paragraph bridging p 25-26). Shimkets et al. specifically contemplate phosphorothioate-based modifications. Shimkets et al. teach their antisense as chimeric RNA-DNA antisense (see for example p 27). Shimkets et al. disclose administering antisense to cells and tissues for the inhibition of the expression of a target nucleic acid, which would necessitate that the antisense be in a composition comprising a pharmaceutically acceptable diluent, e.g. water. Shimkets et al. do not explicitly state that their antisense targets and inhibits the expression of p70 s6 kinase, however, the antisense disclosed by Shimkets et al. meets all of the physical limitations of the instantly claimed antisense and, therefore, would be expected to inherently inhibit the expression of p70 s6 kinase.

Shimkets et al. does not teach modifications to antisense internucleoside linkages and does not teach phosphorothioate linkages. Shimkets et al. does not teach 2'-methoxyethyl sugar modifications or compositions comprising a colloidal dispersion system.

Baracchini et al. teach 2'-O-methoxyethyl sugar modifications, and modified internucleoside linkages, including phosphorothioate linkages, to increase antisense stability and enhance affinity. Baracchini et al. further teach compositions of antisense wherein the composition comprises a comprising a colloidal dispersion system (for example liposomes) for use in delivery of antisense compounds.

It would have been obvious to one of ordinary skill in the art to incorporate the modifications taught by Baracchini et al., including 2'-O-methoxyethyl, and modified internucleoside linkages, including phosphorothioate linkages, into the antisense oligonucleotides taught by Shimkets et al. because such modifications were routine and well known in the art as modifications which enhance the stability, uptake and affinity of an antisense molecule (see for example Baracchini et al. column 6, paragraph 3) and because Shimkets et al. teach incorporating modifications into their antisense which enhance the biological stability or physical stability of these antisense oligonucleotides. It would have been obvious to one of ordinary skill in the art to make a composition comprising said antisense and a pharmaceutically acceptable carrier and a colloidal dispersion system, because pharmaceutically acceptable carriers, including colloidal dispersion systems (e.g. liposomes) were well known in the art for use with antisense molecules as a means to deliver antisense molecules to cells *in vitro* (cell culture), as evidenced by Baracchini et al., and Shimkets et al. set forth their antisense for use in delivery to cells in vitro.

One of ordinary skill in the art would have been motivated to incorporate the modifications taught by Baracchini et al. into the oligonucleotides taught by Shimkets et al. for the benefits of stability and improved hybridization and because Shimkets et al. suggest incorporating any modifications into their antisense which provide the benefits taught by Baracchini and explicitly contemplate phosphorothioate based modifications. One of ordinary skill in the art would have been motivated to provide the antisense taught by Shimkets et al. in a composition comprising a pharmaceutically acceptable

carrier and a colloidal dispersion system, as taught by Baracchini, to improve the delivery of the antisense taught by Shimkets et al. to cells in vitro.

Therefore, at the time the instant invention was made, the invention of claims 1, 2 and 5-16 would have been obvious to one of ordinary skill in the art, as a whole.

Claims 1, 2 and 5-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yang et al. (Endocrinology 142(8): 3502-3511) in view of Baracchini et al.

Claims 1, 2 and 5-16 are drawn to an antisense compound 8-50 nucleotides in length targeted to a nucleic acid encoding p70 s6 kinase (SEQ ID NO:3), wherein the antisense comprises modified bases, including 5-methylcytosine modifications, modified sugars, including 2'-O-methoxyethyl modifications, internucleoside linkage modifications, including phosphorothioate, chimeric antisense, and compositions comprising said antisense and a pharmaceutically acceptable carrier, including a colloidal dispersion system. The claims are further drawn to methods to inhibit the expression of p70 s6 kinase in cells *in vitro*.

Yang et al. teach a 21-mer antisense oligonucleotide targeted to a nucleic acid encoding p70 s6 kinase (SEQ ID NO:3) (see for example (p 3503, last paragraph, to p 3505) and further teach using this antisense in a composition comprising a colloidal dispersion system, lipofectin, to inhibit the expression of p70 s6 kinase in cells in vitro.

Yang et al. do not teach antisense targeted to p70 s6 kinase wherein the antisense comprises a modified internucleoside linkage, including a phosphorothioate

linkage, a modified sugar, including a 2'-O-methoxyethyl sugar moiety, a modified nucleobases, including a 5-methylcytosine, or chimeric antisense.

Baracchini et al. teach 2'-O-methoxyethyl sugar modifications, 5-methyl cytosine base modifications, chimeric oligonucleotides and modified internucleoside linkages, including phosphorothioate linkages, to increase antisense stability and enhance affinity and antisense oligonucleotides of 8-30 nucleotides in length. Baracchini et al. further teach pharmaceutical carriers and colloidal dispersion systems (for example liposomes) for use in delivery of antisense compounds.

It would have been obvious to incorporate the modifications taught by Baracchini et al., including 2'-O-methoxyethyl, 5-methyl cytosine, chimeric oligonucleotides and modified internucleoside linkages, including phosphorothioate linkages, into the antisense molecule taught by Yang et al., because such modifications were routine and well known in the art as modifications which enhance the stability, uptake and affinity of an antisense molecule (see for example Baracchini et al. column 6, paragraph 3) when used to inhibit the expression of a target nucleic acid in cells, which is the purpose set forth by Yang et al. It would have been obvious to one of ordinary skill in the art to make a composition comprising the antisense taught by Yang et al. and a pharmaceutically acceptable carrier, including a colloidal dispersion system, because pharmaceutically acceptable carriers, including colloidal dispersion systems (e.g. liposomes) were well known in the art for use with antisense molecules as a means to deliver antisense molecules to cells *in vitro* (cell culture), as evidenced by Baracchini et

al. and because Yang et al. teach their antisense in a composition with one particular colloidal dispersion system, lipofectin.

One of ordinary skill in the art would have been motivated to incorporate the modifications taught by Baracchini et al. into the antisense taught by Yang et al. for the benefits of stability and improved hybridization. One of ordinary skill in the art would have been motivated to provide the antisense taught by Yang et al. in a composition comprising a pharmaceutically acceptable carrier and a colloidal dispersion system, as taught by Baracchini, to improve the delivery of the antisense taught by Yang et al. to cells in vitro.

Therefore, the invention of claims 1, 2 and 5-16 would have been obvious to one of ordinary skill in the art, as a whole, at the time the instant invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Thursday 8:30-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
April 29, 2003

KAREN LACOURCIERE
PATENT EXAMINER